Use of biomarkers or echocardiography in pulmonary embolism: the Swiss Venous Thromboembolism Registry

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Abstract: BACKGROUND: Cardiac biomarkers and echocardiography for assessing right ventricular function are recommended to risk stratify patients with acute non-massive pulmonary embolism (PE), but it remains unclear if these tests are performed systematically in daily practice.Design and methods: Overall, 587 patients with acute non-massive PE from 18 hospitals were enrolled in the Swiss Venous Thromboembolism Registry (SWIVTER): 178 (30%) neither had a biomarker test nor an echocardiographic evaluation, 196 (34%) had a biomarker test only, 47 (8%) had an echocardiogram only and 166 (28%) had both tests. RESULTS: Among the 409 (70%) patients with biomarkers or echocardiography, 210 (51%) had at least one positive test and 67 (16%) had positive biomarkers and right ventricular dysfunction. The ICU admission rates were 5.1% without vs. 5.6% with testing (P = 0.78), and thrombolysis or embolectomy were performed in 2.8% vs. 4.9%, respectively (P = 0.25). In multivariate analysis, syncope [odds ratio (OR): 3.49, 95% confidence interval (CI): 1.20-10.15; P = 0.022], tachycardia (OR: 2.31, 95% CI: 1.37-3.91; P = 0.002) and increasing age (OR: 1.02; 95% CI: 1.01-1.04; P < 0.001) were associated with testing of cardiac risk; outpatient status at the time of PE diagnosis (OR: 2.24, 95% CI: 1.49-3.36; P < 0.001), cancer (OR: 1.81, 95% CI: 1.17-2.79; P = 0.008) and provoked PE (OR: 1.58, 95% CI: 1.05-2.40; P = 0.029) were associated with its absence. CONCLUSION: Although elderly patients and those with clinically severe PE were more likely to receive a biomarker test or an echocardiogram, these tools were used in only two-thirds of the patients with acute non-massive PE and rarely in combination.

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Summary

Background: Cardiac biomarkers and echocardiography for assessing right ventricular function are recommended to risk stratify patients with acute non-massive pulmonary embolism (PE), but it remains unclear if these tests are performed systematically in daily practice.

Design and methods: Overall, 587 patients with acute non-massive PE from 18 hospitals were enrolled in the Swiss Venous Thromboembolism Registry (SWIVTER): 178 (30%) neither had a biomarker test nor an echocardiographic evaluation, 196 (34%) had a biomarker test only, 47 (8%) had an echocardiogram only and 166 (28%) had both tests.

Results: Among the 409 (70%) patients with biomarkers or echocardiography, 210 (51%) had at least one positive test and 67 (16%) had positive biomarkers and right ventricular dysfunction. The ICU admission rates were 5.1% without vs. 5.6% with testing ($P=0.78$), and thrombolysis or embolectomy were performed in 2.8% vs. 4.9%, respectively ($P=0.25$). In multivariate analysis, syncope [odds ratio (OR): 3.49, 95% confidence interval (CI): 1.20–10.15; $P=0.022$], tachycardia (OR: 2.31, 95% CI: 1.37–3.91; $P=0.002$) and increasing age (OR: 1.02; 95% CI: 1.01–1.04; $P<0.001$) were associated with testing of cardiac risk; outpatient status at the time of PE diagnosis (OR: 2.24, 95% CI: 1.49–3.36; $P<0.001$), cancer (OR: 1.81, 95% CI: 1.17–2.79; $P=0.008$) and provoked PE (OR: 1.58, 95% CI: 1.05–2.40; $P=0.029$) were associated with its absence.

Conclusions: Although elderly patients and those with clinically severe PE were more likely to receive a biomarker test or an echocardiogram, these tools were used in only two-thirds of the patients with acute non-massive PE and rarely in combination.

Introduction

Annually, pulmonary embolism (PE) accounts for more than 100 000 deaths in the USA[1] and 330 000 deaths in Europe,[2] with right ventricular (RV) dysfunction as the most common cause of early mortality.[3] In PE patients who present with preserved systemic pressure and without signs of cardiogenic shock,

common clinical signs of RV dysfunction include tachycardia, hypoxia and distended jugular veins. The electrocardiogram may reveal signs of RV strain, including right bundle branch block, the SI–QIII type or inverted T waves in the precordial leads.[4] However, the assessment of RV function is often unreliable based on the initial clinical evaluation. For risk stratification of hemodynamically stable PE patients, current consensus guidelines of the European Society of Cardiology[5] and the American Heart Association[6] recommend routine assessment of RV function by cardiac biomarkers and/or echocardiography.

Although patients with normal levels of cardiac biomarkers or with preserved RV function on echocardiography have an excellent early prognosis,[7,8] positive biomarker tests or RV dysfunction are strong predictors of adverse clinical outcomes.[9–12] In the Swiss Venous Thromboembolism Registry (SWIVTER), cardiac troponin testing provided incremental prognostic information on top of the initial clinical evaluation with the simplified PE Severity Index (sPESI).[13] Current consensus guidelines from the European Society of Cardiology[5] and the American Heart Association[6] recommend the administration of reperfusion therapy, including thrombolysis, catheter intervention or surgical embolectomy in selected PE patients at increased risk of death.

This study was performed to investigate how frequently cardiac risk stratification tests are being performed in hemodynamically stable patients with acute PE and to compare clinical characteristics and treatment modalities between patients with and without cardiac risk stratification.

Methods

Patients

Four Swiss academic and 14 non-academic acute care hospitals representatively distributed over the country enrolled 644 consecutive patients with acute PE in the prospective SWIVTER between January 2009 and May 2010. Inclusion criteria were age $\geqslant$18 years and objectively confirmed acute PE. There were no exclusion criteria in SWIVTER. Department chiefs of participating hospitals were invited to participate in SWIVTER for enrolling consecutive patients with acute PE. Eligible patients were enrolled at the time of PE diagnosis and registered directly by treating physicians or dedicated study personal at medical or surgical wards or at the emergency department of participating hospitals. Patient informed consent was waived, and anonymous data were entered by treating physicians or dedicated study personal directly from the patient chart into an electronic case report form. PE diagnosis had to be objectively confirmed by contrast-enhanced chest computed tomography, ventilation perfusion scintigraphy or conventional pulmonary angiography. For the present analysis, we excluded 39 (6%) patients with massive PE, defined as systolic systemic pressure of <90 mm Hg, and 18 (3%) patients treated on an outpatient basis without follow-up data of whom one patient had an increased sPESI. Overall, 587 (91%) patients with acute non-massive PE were included in our analysis. In accordance with local regulations, the study was approved by the local ethics committees of participating hospitals.

Data and definitions

Two study groups were formed: patients with cardiac risk stratification and patients without cardiac risk stratification. Cardiac risk stratification was defined as the presence of a biomarker test result or an echocardiographic evaluation for assessing RV function within 24 h of PE diagnosis. SWIVTER did not issue recommendations on the indications of biomarker testing and echocardiography.

Biomarker testing was performed in the central laboratory of participating hospitals. Test results were taken from laboratory slips. Accepted biomarker tests included conventional troponin I (Beckman Coulter TnI, cut-off: 0.09 µg/l), conventional (Roche Elecsys cTnT, cut-off: 0.1 µg/l) or highly sensitive (Roche Elecsys cTnT-hs, cut-off: 0.014 µg/l) troponin T and B-type natriuretic peptide (BNP, Alere Triage BNP, cut-off: 100 pg/ml). A positive biomarker test was defined as a biomarker level above the mentioned assay thresholds.

Standard transthoracic echocardiography was performed and interpreted by a local cardiologist. Data on RV function were taken from echocardiographic reports. There was no central adjudication of echocardiographic images in SWIVTER, but RV dysfunction on echocardiography was predefined and diagnosed from participating centers if at least one of the following signs was present: RV dimension >30 mm in the parasternal long axis, right-to-left ventricular dimension ratio >0.9 in the apical four-chamber view, moderate or severe systolic RV dysfunction, tricuspid systolic velocity >2.6 m/s, septal flattening or paradoxical septal motion.

Non-massive PE was defined as systemic blood pressure of $\geqslant$90 mm Hg. Provoked PE was defined according to the guidelines of the American College of Chest Physicians as PE associated with surgery,

hospitalization, immobilization for more than 3 days, estrogen therapy, pregnancy or prolonged travel of >5 h, all within 30 days prior to PE diagnosis.[14] An increased sPESI was defined as presence of at least one of the following criteria: age >80 years, systemic systolic pressure <100 mmHg, heart rate >110 beats/min, oxygen saturation <90%, cancer, heart failure or chronic lung disease.[15]

A standardized electronic case report form was used for the collection of anonymous data on patient demographics, hospital status at the time of PE diagnosis, clinical presentation, thrombosis localization and risk factors, cardiac risk stratification test results, treatment and 30-day clinical outcomes including mortality, symptomatic objectively confirmed recurrent PE and bleeding requiring medical attention. Overall, 499 (85%) patients had completed 30-day follow-up, 76 (13%) had follow-up data for a minimum of 15 days and 12 (2%) for <15 days.

Statistical analysis

For comparison of clinical characteristics and treatment modalities between patients with and without cardiac risk stratification, we analyzed patient demographics, acute and chronic comorbidities, clinical markers of PE severity, anticoagulation therapy and reperfusion therapy, including thrombolysis, catheter interventions and surgical embolectomy. For these analyses, group comparisons for continuous variables with a normal distribution were performed by *t*-test, for continuous variables with a skewed distribution by a rank sum test and for discrete variables by the chi square or Fisher's exact test.

Univariate logistic regression analysis reporting odds ratios (OR) with 95% confidence intervals (CI) was conducted to identify clinical factors associated with cardiac risk stratification. Subsequently, multivariate logistic regression analysis was performed to identify clinical factors associated with cardiac risk stratification. Univariate predictors with a P value < 0.05 were entered in the regression model, and a backward elimination procedure was used to stepwise discard variables without significance. All reported P values are two tailed. Data were analyzed using STATA 10 software (STATACorp LP, College Station, TX, USA).

Results

Patient characteristics

Overall, 178 (30%) patients neither had a cardiac biomarker test nor an echocardiographic evaluation, 196 (34%) had a biomarker test only, 47 (8%) had an echocardiogram only and 166 (28%) had both tests. Among the 409 (70%) patients with biomarkers or echocardiography, 210 (51%) had at least one positive test and 67 (16%) had positive biomarkers and RV dysfunction on echocardiogram (Figure 1).

In comparison to patients with cardiac risk stratification, patients without cardiac risk stratification were younger, more often outpatient at the time of PE diagnosis and more frequently had provoked or cancer-associated PE (Table 1). Patients without cardiac risk stratification less frequently had hypoxia, tachycardia, syncope, embolism of the pulmonary main stem or the main pulmonary arteries, right heart strain on electrocardiography and an increased sPESI than patients with cardiac risk stratification.

Overall, 264 (45%) patients were treated in academic and 323 (55%) in non-academic centers. There was no difference in the use of cardiac risk stratification between academic vs. non-academic centers (69% vs. 70%; $P=0.73$). Among patients with cardiac risk stratification, a positive biomarker test or RV dysfunction was more often present in patients from non-academic vs. academic centers (56% vs. 46%; $P=0.038$). There was no difference in the proportion of patients with an increased sPESI (65% vs. 69%; $P=0.33$) and with main stem or main pulmonary artery embolism (34% vs. 33%; $P=0.78$) between non-academic and academic centers.

Treatment of VTE

In comparison to patients with cardiac risk stratification, patients without cardiac risk stratification less often were treated on an inpatient basis and less frequently received systemic thrombolysis (Table 1). However, any reperfusion therapy, including systemic thrombolysis, catheter intervention or surgical embolectomy, was similarly often used in patients with and without cardiac risk stratification. The ICU admission rate was also similar in patients with vs. without cardiac risk stratification.

Among the 166 patients with biomarker testing and echocardiography, the hospitalization rates were 100% in patients with positive biomarkers plus RV dysfunction and 96% in patients without any positive test result ($P=0.08$); the ICU admission rates were similar (4.5% vs. 4.4%; $P=0.99$), and there was more frequent use of reperfusion therapy (14.9% vs. 2.2%; $P=0.027$), respectively.

Patients from academic centers were less often hospitalized (86% vs. 92%; $P=0.010$), more frequently received reperfusion therapy (7.2% vs. 1.9%; $P=0.001$) and more often were admitted to

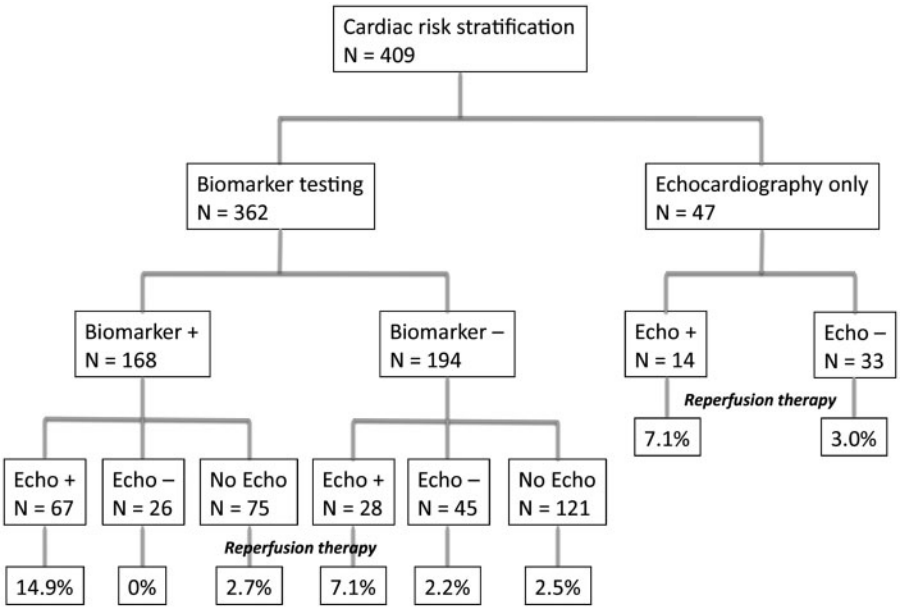

Figure 1. Biomarker testing and echocardiographic results with rates of reperfusion therapy. biomarker +, positive cardiac biomarker; biomarker –, negative cardiac biomarker; echo +, RV dysfunction on echocardiography; echo –, no RV dysfunction on echocardiography; no echo, echocardiography not available.

the ICU (9% vs. 3%; $P=0.002$) than those from non-academic centers.

The overall rate of cumulative 30-day mortality was 3.2%, the combined rate of 30-day mortality or recurrent PE 4.4% and the rate of 30-day bleeding requiring medical attention 4.6%. There was no significant difference in the combined rate of 30-day mortality or recurrent PE between academic vs. non-academic centers (5.9% vs. 3.2%; $P=0.13$).

Predictors of the use of cardiac risk stratification

In multivariate analysis, syncope, tachycardia and increasing age were associated with testing of cardiac risk; outpatient status at the time of PE diagnosis, cancer and provoked PE were associated with its absence (Table 2).

Discussion

In SWIVTER, cardiac biomarkers and echocardiography were used in only two-thirds of the patients with acute non-massive PE and rarely in combination. Elderly patients and those with clinically severe PE were more likely to receive a biomarker test or an echocardiogram.

Cardiac risk stratification was associated with a higher proportion of inpatient treatment and an increased use of systemic thrombolysis as compared to patients without cardiac risk assessment. However, only a minority of patients (7%) with at least one positive test result received reperfusion therapy, suggesting that cardiac risk stratification test results were rarely used to guide management decisions. These findings may be explained by the fact that to date no convincing outcome data are available to support the use of reperfusion therapy for hemodynamically stable PE patients with biochemical or echocardiographic evidence of RV dysfunction.

Our study identified several factors associated with absent testing of cardiac risk. Patients without cardiac risk stratification were younger and more often outpatient at the time of diagnosis and had clinically and anatomically less severe PE. In contrast, other patients without cardiac risk stratification had important comorbidities as reflected by a greater proportion of patients with an increased sPESI as compared to patients with cardiac risk stratification. Obviously, physicians often abstained from ordering biomarker tests or echocardiography in two distinct risk scenarios: prognosis was likely estimated as being poor in the presence of cancer and other severe comorbidities, and it was estimated as being favorable in case of younger age or clinically less severe PE.

In our study, patient characteristics, comorbidities and clinical findings were consistent with other studies on patients with acute non-massive PE.[16,17] The proportion of patients with an increased sPESI in our study (66%) and in the validation study (69%) was similar.[15] Overall, 90% of the patients were

Table 1 Demographics, comorbidities, clinical findings and VTE therapy

	Total ($N=587$)	Cardiac risk stratification ($N=409$)	No cardiac risk stratification ($N=178$)	P
Demographics				
Age, mean years ± SD	65 ± 16	67 ± 16	61 ± 18	<0.001
Age >80 years, *n* (%)	105 (17.9)	81 (19.8)	24 (13.5)	0.07
Women, *n* (%)	273 (46.5)	198 (48.4)	75 (42.1)	0.16
Inpatient at the time of diagnosis, *n* (%)	301 (48.7)	188 (54.0)	113 (36.5)	<0.001
Duration of hospital stay, median days (IQR)	10 (6–19)	10 (6–17)	13 (7–26)	0.017
Comorbidities				
Cancer, n (%)	149 (25.4)	92 (22.5)	57 (32.0)	0.015
Prior thromboembolism, *n* (%)	143 (24.4)	98 (24.0)	45 (25.3)	0.73
Bed rest for >3 days within 30 days, *n* (%)	99 (16.9)	60 (14.7)	39 (21.9)	0.031
Chronic lung disease, *n* (%)	85 (14.5)	53 (13.0)	32 (18.0)	0.11
Obesity, *n* (%)	84 (14.3)	64 (15.7)	20 (11.2)	0.16
Surgery within 30 days, *n* (%)	74 (12.6)	49 (12.0)	25 (14.0)	0.49
Acute respiratory failure, *n* (%)	47 (8.0)	35 (8.6)	12 (6.7)	0.46
Congestive heart failure, *n* (%)	45 (7.7)	36 (8.8)	9 (5.1)	0.12
Ongoing chemotherapy, *n* (%)	41 (7.0)	23 (5.6)	18 (10.1)	0.050
ICU admission, *n* (%)	32 (5.5)	23 (5.6)	9 (5.1)	0.78
Prior bleeding requiring medical attention within 30 days, *n* (%)	29 (4.9)	17 (4.2)	12 (6.7)	0.18
Thrombocytopenia, *n* (%)	17 (2.9)	9 (2.2)	8 (4.5)	0.13
Clinical findings				
Dyspnea, *n* (%)	483/584 (82.7)	351/408 (86.0)	132/176 (75.0)	0.001
Right heart strain on ECG, *n* (%)	204/448 (45.5)	177/363 (48.8)	27/85 (31.8)	0.005
Provoked PE, *n* (%)	218 (37.1)	138 (33.7)	80 (44.9)	0.010
Thrombosis of main stem or main pulmonary arteries, *n* (%)	197 (33.6)	151 (36.9)	46 (25.8)	0.009
Oxygen saturation in room air <90%, *n* (%)	146/526 (27.8)	112/364 (30.8)	34/162 (21.0)	0.021
Heart rate ⩾110 beats/min, *n* (%)	130/563 (23.1)	107/396 (27.0)	23/167 (13.8)	0.001
Syncope, *n* (%)	44/584 (7.5)	40/408 (9.8)	4/176 (2.3)	0.002
Increased sPESI, *n* (%)	390 (66.4)	285 (69.7)	105 (59.0)	0.012
Therapy				
Inpatient therapy, *n* (%)	524 (89.3)	381 (93.2)	143 (80.3)	<0.001
Reperfusion therapy,[a] *n* (%)	25 (4.3)	20 (4.9)	5 (2.8)	0.25
Systemic thrombolysis, *n* (%)	13 (2.2)	13 (3.2)	0 (0.0)	0.016
Catheter therapy, *n* (%)	8 (1.4)	6 (1.5)	2 (1.1)	0.74
Surgical thrombectomy, *n* (%)	7 (1.2)	4 (1.0)	3 (1.7)	0.47
Inferior vena cava filter, *n* (%)	14 (2.4)	10 (2.4)	4 (2.3)	0.89
Planned duration of anticoagulation				
⩽3 months, *n* (%)	38 (6.5)	23 (5.6)	15 (8.4)	0.20
>3–12 months, *n* (%)	374 (63.7)	259 (63.3)	115 (64.6)	0.77
>12 months or indefinite, *n* (%)	175 (29.8)	127 (31.1)	48 (27.0)	0.32

[a]Some patients had a combination of systemic thrombolysis, catheter therapy or surgical thrombectomy
VTE, venous thromboembolism; ICU, intensive care unit; sPESI, simplified Pulmonary Embolism Severity Index.

managed in-hospital in our study. However, this proportion will possibly decline in the future because outpatient management is feasible and safe according to a recent randomized trial on outpatient management of low-risk PE patients.[18]

One strength of our study is the prospective enrollment of consecutive patients with acute non-massive PE and the systematic collection of information on biomarker test results, echocardiographic evaluation and medical management. To the best of our knowledge, SWIVTER is the first study to evaluate the use of cardiac risk stratification in routine clinical practice. One study limitation is that there was no central adjudication of echocardiographic test results, and quality of echocardiography and its interpretation may have varied between centers. As timing of cardiac risk stratification tests and management decisions was not

Table 2 Clinical factors associated with absent testing of cardiac risk ($N = 560$)

Analysis	Univariate		Multivariate	
Factor	OR (95% CI)	*P*	OR (95% CI)	*P*
Outpatient at the time of PE diagnosis	2.04 (1.42–2.93)	<0.001	2.24 (1.49–3.36)	<0.001
Cancer	1.62 (1.10–2.40)	0.015	1.81 (1.17–2.79)	0.008
Provoked PE	1.60 (1.11–2.30)	0.010	1.58 (1.05–2.40)	0.029
Age, per year	0.98 (0.97–0.99)	<0.001	0.98 (0.97–0.99)	<0.001
Heart rate ⩾ 110 beats/min	0.43 (0.26–0.71)	0.001	0.43 (0.26–0.73)	0.002
Syncope	0.21 (0.08–0.61)	0.004	0.29 (0.10–0.83)	0.022

captured, it was not possible to investigate the effect of risk stratification test results on management decisions, particularly on outpatient versus inpatient management. The large ongoing PE International Thrombolysis (PEITHO, ClinicalTrials.gov Identifier: NCT00639743) trial on patients with biochemical and imaging evidence of RV dysfunction will help answering the question whether there is a role for routine cardiac risk stratification followed by reperfusion therapy in this setting.

In summary, biochemical or imaging tests indicating RV dysfunction were used in only two-thirds of the patients with acute non-massive PE, and such testing was not associated with more aggressive management, including admission to the ICU or administration of reperfusion treatment.

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